MAJOR ARTICLE

Seroprevalence of Human Herpesvirus 8 among Injection Drug Users in San Francisco

Jonnae Atkinson,[1] Brian R. Edlin,[3] Eric A. Engels,[1] Alex H. Kral,[3] Karen Seal,[3] Christine J. Gamache,[2] Denise Whitby,[2] and Thomas R. O'Brien[1]

[1]Viral Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, and [2]Viral Epidemiology Section, Science Applications International Corporation—Frederick, Frederick, Maryland; [3]Urban Health Study, University of California, San Francisco

The association between injection drug use and human herpesvirus 8 (HHV-8) was examined to investigate bloodborne transmission of the virus. In all, 1905 injection drug users (IDUs) enrolled in a cross-sectional study were tested for K8.1 antibodies to HHV-8 lytic antigen. Logistic regression was used to adjust for demographic and sexual behavior variables. HHV-8 seroprevalence was 10% among women, 10% among heterosexual men, and 23% among men who have sex with men. In adjusted analyses, HHV-8 seroprevalence increased with longer duration of injection drug use for each of these groups ($P = .01$, $P = .03$, and $P = .049$ for trend, respectively). HHV-8 infection is relatively common among IDUs in San Francisco, and longer duration of injection drug use is associated with an increase in the risk of HHV-8 infection that is not explained by sexual behavior or demographic differences. These results are consistent with the occurrence of bloodborne transmission of HHV-8 among IDUs.

Human herpesvirus 8 (HHV-8), also known as "Kaposi sarcoma–associated herpesvirus," is an oncogenic virus that is associated with Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease [1–4]. The high seroprevalence and seroincidence of HHV-8 among US men who have sex with men (MSM) [5–7] suggest that the primary mode of transmission of HHV-8 in the United States is sexual contact between men.

The evidence for bloodborne transmission of HHV-8 is mixed. Transmission via blood transfusion has not been found so far [8, 9], and studies of HHV-8 infection and injection drug use have yielded inconsistent results. Some studies have found an association with frequency of drug injection [10–12], but a recently published investigation of HHV-8 in Dutch injection drug users (IDUs) found little evidence that HHV-8 is transmitted through drug injection [13].

In this study, we examined data and serum samples from street-recruited IDUs in the San Francisco Bay area, including women, heterosexual men, and MSM. The purpose of this study was to determine whether the duration of injection drug use, a marker for bloodborne exposures, was associated with HHV-8 infection independently of sociodemographic and sexual risk factors.

SUBJECTS, MATERIALS, AND METHODS

Subjects. The study population consisted of participants in the Urban Health Study (University of Cali-

Received 26 August 2002; accepted 18 November 2002; electronically published 6 March 2003.

Financial support: Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health (contract N01-CO-12400).

Presented in part: 5th International Workshop on Kaposi-Sarcoma–Associated Herpesvirus and Related Agents, Kloster Irsee, Germany, 7–11 August 2002.

Informed consent was obtained from each study participant. The study was approved by the Committee on Human Subjects Research at the University of California, San Francisco, and the institutional review board of the National Cancer Institute. The experimentation guidelines of all institutions and of the US Department of Health and Human Services were followed in conducting the clinical research.

Reprints or correspondence: Dr. Thomas R. O'Brien, Viral Epidemiology Branch, Div. of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd., Rm. 8016, MSC 7248, Rockville, MD 20852 (obrient@exchange.nih.gov).

The Journal of Infectious Diseases 2003;187:974–81

0022-1899/2003/18706-0012$15.00

fornia, San Francisco). Every month, Urban Health Study investigators recruit active IDUs from street settings in 1 of 6 inner-city San Francisco Bay area neighborhoods, which are visited in rotation [14]. All individuals ⩾18 years of age who have a history of drug injection in the past 30 days are eligible for enrollment. Potential subjects are not required to disclose their names to participate. New participants are screened for visible signs of recent or chronic injection (i.e., "track mark" scars or recently punctured veins). They receive modest monetary compensation for each study visit and are eligible for subsequent study visits, regardless of whether they continue to use injection drugs.

Trained staff obtain informed consent, interview participants, counsel them on reducing infection risks, and refer them to appropriate medical and social services. Participants are asked about their injection drug use history, including age at first injection, number of injections in the past 30 days, type of drugs injected, use of shared needles, and needle-cleaning methods. Questions related to sexual behavior include sexual orientation, whether the subject has a current steady sex partner, injection drug use history of the sex partner, and number of different sex partners in the past 6 months. In addition, participants are asked whether they have ever engaged in sexual activity with someone of the same sex and whether they have ever performed sex acts in exchange for money or drugs. Blood samples are collected from participants by a phlebotomist. Further details about the Urban Health Study are provided elsewhere [14, 15].

For the present study, data and plasma samples collected between 1998 and 2000 were examined cross-sectionally. Because subjects may anonymously participate in subsequent surveys, participants with similar demographic information were identified and evaluated by AmpFLSTR Profiler Plus PCR Amplification kit (PE Applied Biosystems), which differentiates persons on the basis of 9 short tandem repeat loci and the amelogenin locus in a single reaction tube. Subjects who responded more than once were eliminated from the analysis. Data from women, heterosexual men, and MSM were examined separately, because these groups may have different risks of acquiring HHV-8 infection through sex [10,16,17]. MSM included men who reported either a homosexual or bisexual orientation or ever having sex with a man. Men not defined as "MSM" were categorized as "heterosexual." To further control for the possibility of homosexual contact among men categorized as heterosexual, a secondary analysis was performed that excluded men who reported receiving cash or drugs in exchange for sex.

Serologic analysis. A second-generation ELISA was used to detect HHV-8 antibodies directed against the K8.1 lytic antigen. In brief, *Escherichia coli*–expressed K8.1 recombinant protein was diluted 1:5000 in 0.05 *M* carbonated/bicarbonate buffer solution at pH 10.0. Serum and plasma samples were diluted 1:20. A sample was considered to be seropositive if the OD was >1.0. The sensitivity and specificity of this test in other studies ranged from 78% to 100% and from 94% to 100%, respectively [18, 19].

Samples were tested for human immunodeficiency virus type 1 (HIV-1) infection by an EIA (Bio-Rad), and reactive samples were confirmed by HIV-1 Western blot (Cambridge Biotech). Hepatitis C virus (HCV) infection was detected using a third-generation EIA (Ortho). Antibodies to hepatitis B virus (HBV) core antigen were detected by radioimmunoassay (CORAB; Abbott Laboratories).

Statistical analysis. First, we used logistic regression in univariate analysis to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between HHV-8 infection and selected sociodemographic, sexual, injection drug use, and medical risk factors within each of the 3 groups. Next, potential confounding variables were identified, and adjusted ORs were calculated. A variable was considered to be a confounding variable if its inclusion in the logistic model changed the OR by ⩾15% [20]. HIV-1 is both bloodborne and sexually transmitted and is a potential source of morbidity in these subjects. Because the potential relationship between HIV-1 and HHV-8 is complex, adjustment for HIV-1 infection status was limited to secondary analyses.

We examined potential linear trends for variables with ordered levels (i.e., age, number of sexual partners, and duration of injection drug use) and heterogeneity for unordered variables by maximum likelihood methods [21]. We selected cutoff points for categorized variables that had biologic meaning and increased statistical stability. Age categories for women and MSM were collapsed from <30, 30–39, 40–49, 50–59, and ⩾60 years to <30, 30–39, 40–49, and ⩾50 years to calculate *P* values for trends because of the small number of participants >60 years of age (6 women and 9 MSM). Similarly, duration of injection drug use categories were collapsed from ⩽10, 11–20, 21–30, 31–40, and ⩾41 years to ⩽10, 11–20, 21–30, and ⩾31 years for women and MSM because of the small number of participants who had an injection drug use history of >40 years (1 woman and 3 MSM). Because our objective was to examine linear trends related to duration of injection drug use, we did not collapse age and duration of injection drug use categories for heterosexual men. Selected variables, including age and duration of injection drug use, were also evaluated continuously, with similar results (data not shown). Analyses were conducted using SAS software (version 8.0; SAS Institute).

RESULTS

Demographic characteristics. The study consisted of 1905 IDUs, including 556 women, 1074 heterosexual men, and 275 MSM (table 1). Sociodemographically, the risk groups differed

Table 1. Distribution of sociodemographic, sexual, drug use, and viral infection characteristics, by human herpes virus 8 (HHV-8) risk group, among 1905 injection drug users in San Francisco.

Characteristic	Women (n = 556)	Heterosexual men (n = 1074)	MSM (n = 275)	P[a]
Sociodemographic				
Race/ethnicity				
African-American	301 (54)	575 (54)	74 (27)	
White, non-Hispanic	187 (34)	373 (35)	161 (59)	
Hispanic	24 (4)	73 (7)	14 (5)	
Other	44 (8)	53 (5)	26 (9)	<.001
Age, mean years ± SD	41.8 ± 8.8	45.3 ± 9.0	40.0 ± 9.5	<.001
Age group				
<30 years	60 (11)	66 (6)	39 (14)	
30–39 years	126 (23)	171 (16)	98 (36)	
40–49 years	284 (51)	511 (48)	96 (35)	
50–59 years	79 (14)	277 (26)	33 (12)	
⩾60 years	6 (1)	49 (5)	9 (3)	<.001
Sexual behaviors				
No. of sex partners in the past 6 months				
None	149 (28)	321 (30)	152 (57)	
1	237 (44)	478 (45)	47 (17)	
2–3	68 (13)	153 (14)	30 (11)	
⩾4	82 (15)	119 (11)	40 (15)	<.001
Steady sex partner uses injection drugs	347 (62)	493 (46)	89 (32)	<.001
Ever received cash for sex	284 (51)	138 (13)	176 (64)	<.001
Ever received drugs for sex	124 (22)	103 (10)	117 (43)	<.001
Drug use				
Age first injected any drug, mean years ± SD	22.2 ± 7.6	20.3 ± 7.1	20.5 ± 7.7	<.001
Duration of injection drug use, mean years ± SD	19.0 ± 10.0	25.0 ± 10.9	19.4 ± 10.4	<.001
Duration of injection drug use				
⩽10 years	137 (25)	133 (12)	61 (22)	
11–20 years	144 (26)	189 (18)	84 (31)	
21–30 years	199 (37)	390 (37)	82 (30)	
31–40 years	64 (12)	295 (28)	43 (16)	
>40 years	1 (<1)	58 (5)	3 (1)	<.001
No. of times injected drugs within the past 30 days, mean ± SD	53.4 ± 78.0	62.0 ± 69.8	65.2 ±76.5	.08
Viral infections				
HIV-1	63 (11)	106 (10)	64 (23)	<.001
Hepatitis C virus	511 (92)	974 (91)	239 (88)	.12
Hepatitis B virus	402 (72)	852 (79)	215 (78)	.002

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Data for some variables were missing from some subjects. HIV-1, human immunodeficiency virus type 1; MSM, men who have sex with men.

[a] χ^2 test was used to calculate P for categorized variables. Analysis of variance was used to compare differences between mean values.

by race/ethnicity ($P<.001$) and age ($P<.001$). Most women (54%) and heterosexual men (54%) were African-American, but most MSM (59%) were white (table 1). Participants from all groups frequently reported engaging in high-risk sex. Twenty-eight percent of women, 25% of heterosexual men, and 26% of MSM reported having ⩾2 sex partners in the past 6 months, and 62% of women, 46% of heterosexual men, and 32% of MSM had a steady sex partner who injected drugs. In contrast, reports of having received cash or drugs in return for sex varied markedly between the groups. Such reports were frequent from MSM (cash, 64%; drugs, 43%) and women (cash, 51%; drugs, 22%) but not from heterosexual men (cash, 13%; drugs, 10%).

Most participants reported a long history of injection drug

Table 2. Human herpesvirus 8 (HHV-8) seroprevalence, unadjusted odds ratios (ORs), and 95% confidence intervals (CIs), by potential risk factors and HHV-8 risk group, among 1905 injection drug users in San Francisco.

Risk factor	Women (n = 556)			Heterosexual men (n = 1074)			MSM (n = 275)		
	HHV-8 positive, n/N (%)	OR (95% CI)	P[a]	HHV-8 positive, n/N (%)	OR (95% CI)	P[a]	HHV-8 positive, n/N (%)	OR (95% CI)	P[a]
Total	53/556 (10)			103/1074 (10)			62/275 (23)		
Race/ethnicity									
African-American	33/301 (11)	1.0	.53	63/575 (11)	1.0	.05	19/74 (26)	1.0	.57
White, non-Hispanic	16/187 (9)	0.8 (0.4–1.4)		31/373 (8)	0.7 (0.5–1.2)		35/161 (22)	0.8 (0.4–1.5)	
Hispanic	2/24 (8)	0.8 (0.2–3.3)		8/73 (11)	1.0 (0.5–2.2)		2/14 (14)	0.5 (0.1–2.4)	
Other	2/44 (5)	0.4 (0.1–1.7)		1/53 (2)	0.2 (0.0–1.2)		6/26 (23)	0.9 (0.3–2.5)	
Age group									
<30 years	6/60 (10)	1.0	.64	3/66 (5)	1.0	.36	6/39 (15)	1.0	.55
30–39 years	9/126 (7)	0.7 (0.2–2.1)		22/171 (13)	3.1 (0.9–0.7)		31/98 (32)	2.5 (1.0–6.7)	
40–49 years	31/284 (11)	1.1 (0.4–2.8)		43/511 (8)	1.9 (0.6–6.4)		16/96 (17)	1.1 (0.4–3.1)	
⩾50 years	7/85 (8)	0.8 (0.3–2.6)		—	—		9/42 (21)	1.5 (0.4–4.7)	
50–59 years	—	—		27/277 (10)	2.3 (0.7–7.7)		—	—	
⩾60 years	—	—		8/49 (16)	4.1 (1.0–16.3)		—	—	
Duration of injection drug use									
⩽10 years	8/137 (6)	1.0	.03	9/133 (7)	1.0	.10	9/61 (15)	1.0	.44
11–20 years	12/144 (8)	1.6 (0.6–4.0)		17/189 (9)	1.5 (0.6–3.4)		24/84 (29)	2.4 (1.0–5.6)	
21–30 years	24/199 (12)	2.4 (1.0–5.5)		38/390 (10)	1.6 (0.8–3.4)		18/82 (22)	1.7 (0.7–4.1)	
⩾31 years	9/65 (14)	2.8 (1.0–7.7)		—	—		11/46 (24)	1.9 (0.7–5.0)	
31–40 years	—	—		30/295 (10)	1.7 (0.8–3.6)		—	—	
>40 years	—	—		9/58 (16)	2.7 (1.0–7.2)		—	—	
No. of sex partners in the past 6 months									
None	20/149 (13)	1.0	.02	29/321 (9)	1.0	.97	28/152 (18)	1.0	.02
1	22/237 (9)	0.7 (0.3–1.2)		51/478 (11)	1.2 (0.7–1.9)		10/47 (21)	1.2 (0.5–2.6)	
2–3	4/68 (6)	0.4 (0.1–1.2)		8/153 (5)	0.5 (0.2–1.2)		8/30 (27)	1.6 (0.6–3.8)	
⩾4	4/82 (5)	0.3 (0.1–1.0)		14/119 (12)	1.3 (0.7–2.6)		14/40 (35)	2.3 (1.1–4.9)	
Steady sex partner uses injection drugs									
Yes	33/347 (10)	1.0 (0.6–1.8)	.98	59/493 (12)	1.7 (1.1–2.5)	.02	19/89 (21)	0.9 (0.5–1.7)	.74
No	20/209 (10)	1.0		44/581 (8)	1.0		43/186 (23)	1.0	
Ever received cash for sex									
Yes	30/284 (11)	1.3 (0.7–2.2)	.41	16/138 (12)	1.3 (0.7–2.2)	.40	42/176 (24)	1.2 (0.7–2.3)	.49
No	23/270 (9)	1.0		87/934 (9)	1.0		20/99 (20)	1.0	
Ever received drugs for sex									
Yes	11/124 (9)	0.9 (0.4–1.8)	.77	9/103 (9)	0.9 (0.4–1.8)	.75	32/117 (27)	1.6 (0.9–2.8)	.11
No	42/431 (10)	1.0		94/968 (10)	1.0		30/157 (19)	1.0	
HIV-1 infection status									
Seropositive	12/63 (19)	2.6 (1.3–5.3)	.006	15/106 (14)	1.6 (0.9–3.0)	.09	28/64 (44)	4.0 (2.2–7.5)	<.0001
Seronegative	41/493 (8)	1.0		88/968 (9)	1.0		34/211 (16)	1.0	

NOTE. HIV-1, human immunodeficiency virus type 1; MSM, men who have sex with men; *n/N,* no. of subjects with HHV-8/no. with risk factor.

[a] P values for trend were calculated for age, no. of sexual partners, and duration of injection drug use, using logistic regression analysis; P values for heterogeneity were calculated for all other variables, using the χ^2 test for heterogeneity.

use. The mean age of first drug injection was 20.3–22.2 years. The mean duration of injection drug use ranged from 19.0 years for women to 25.0 years for heterosexual men; 75% of women, 88% of heterosexual men, and 78% of MSM had injected drugs for >10 years. There was a high seroprevalence of HBV (range, 72%–79%) and HCV (range, 88%–92%) among all subjects. In contrast, fewer subjects were infected with HIV-1, and this virus was considerably more common among MSM (23%) than among either women (11%) or heterosexual men (10%).

Univariate analysis. The seroprevalence of HHV-8 among women was 10% and did not differ by race or age (table 2). HHV-8 infection in women was associated with duration of injection drug use, increasing from 6% among those with 0–10 years of injection drug use to 14% among those with >30 years

of injection drug use ($P = .03$ for trend) (table 2). The odds of HHV-8 infection were inversely related to the number of recent male sex partners ($P = .02$ for trend), but there was no association with other sexual behaviors, including steady involvement with a sex partner who uses injection drugs and receiving money or drugs in exchange for sex. In addition, there was no meaningful difference in the HHV-8 seroprevalence among the 118 women who reported having sex with other women (9.3%) and that among the 438 women who did not (9.7%) (OR, 1.0; 95% CI, 0.5–1.9). The odds of HHV-8 seropositivity were increased 2.6-fold among HIV-1–infected women, compared with HIV-1–uninfected women. The odds of HHV-8 seropositivity were also higher among women who were infected with HCV or HBV, although these differences were not as marked.

HHV-8 seroprevalence among heterosexual men was also 10% (table 2). HHV-8 infection rates among men, like rates among women, did not differ by race/ethnicity or age but increased with duration of injection drug use. The lowest HHV-8 seroprevalence (7%) was observed among heterosexual men with a history of injection drug use of ≤10 years; an intermediate seroprevalence was present among those with a history of 11–40 years (9%–10%); and the highest seroprevalence was seen among those who had been using injection drugs for >40 years (16%) ($P = .10$, test for trend across all categories). The odds of HHV-8 seropositivity did not differ by number of recent sex partners or among those who reported receiving cash in return for sex, but it was increased among heterosexual men who had a steady sex partner who injected drugs (OR, 1.7; 95% CI, 1.1–2.5). The odds of HHV-8 seropositivity were moderately higher among heterosexual men infected with HIV-1 (OR, 1.6; 95% CI, 0.9–3.0) or HBV (OR, 1.7; 95% CI, 1.07–3.1) but not among those infected with HCV.

HHV-8 seroprevalence was significantly higher among MSM (23%) than among women or heterosexual men ($P < .001$ for each comparison; table 2). There was no linear association between HHV-8 seroprevalence and age, but MSM 30–39 years of age were 2.5 times more likely to be seropositive for HHV-8 than were men <30 years of age. In contrast to women and heterosexual men, there was no linear trend between HHV-8 seroprevalence and duration of injection drug use. MSM with a history of ≥11 years of injection drug use were, however, marginally more likely to be infected with HHV-8 than were those with a history of 0–10 years (OR, 1.9; 95% CI, 0.9–4.2). The odds of HHV-8 seropositivity increased with the number of recent sex partners ($P = .02$); the highest odds were seen among MSM who reported having ≥4 male sex partners in the past 6 months (OR, 2.3; 95% CI, 1.1–4.9). HHV-8 status was not associated with any of the other reported sexual behaviors, including having a steady sex partner who uses injection drugs or receiving money or drugs in return for sex. HHV-8 serostatus was strongly associated with HIV-1 seropositivity (OR, 4.0; 95% CI, 2.2–7.5) and weakly associated with HBV seropositivity (OR, 1.6; 95% CI, 0.8–3.4).

Multivariate analysis. We conducted multivariate analyses for each risk group to adjust the association between HHV-8 serostatus and injection drug use for potential confounding variables (table 3). As mentioned earlier, a variable was considered to be a confounding variable if it altered the OR by ≥15%. Among women, HHV-8 seropositivity was more strongly associated with duration of injection drug use after adjustment for age and number of male sex partners ($P = .01$, test for linear trend). In this adjusted analysis, women who had used injection drugs the longest (>30 years) were 5.8-fold more likely to be seropositive for HHV-8 than were those who had used injection drugs for ≤10 years. Adjustment for HIV-1 as a potential confounding variable yielded similar results (data not shown).

The multivariate results for heterosexual men were consistent with those for women. The association between duration of injection and HHV-8 seropositivity was slightly increased ($P = .09$, test for linear trend), compared with the unadjusted analysis. Heterosexual men who had used injection drugs for >40 years were 3.0-fold more likely to be positive for HHV-8 than were those with a history of injection drug use of ≤10 years. Adjustment for HIV-1 serostatus yielded similar results (data not shown). To further control for the potential effect of sexual behavior, we excluded men who reported receiving cash or drugs in exchange for sex ($n = 172$) from the analysis, because men in this group might have engaged in unreported homosexual activity. In this analysis, the HHV-8 seroprevalence increased significantly with duration of injection drug use ($P = .03$ for trend), with an adjusted OR of 4.2 (95% CI, 0.9–19.9) among those with a history of ≥40 years of injection drug use.

Adjustment for confounding variables had a much greater impact on the analysis of data from MSM than from women or heterosexual men. Among MSM, the trend toward higher HHV-8 seroprevalence in association with longer duration of injection drug use increased considerably after adjustment for age and number of male sex partners ($P = .08$ for trend); the adjusted OR for HHV-8 seropositivity among those who had used injection drugs for >30 years was 3.9 (95% CI, 1.1–14.4). Adjustment for HIV-1 serostatus further strengthened this association ($P < .05$ for trend). The results of that analysis were as follows: injection drug use history of 11–20 years, OR of 2.9 (95% CI, 1.1–7.9); 21–30 years, OR of 2.8 (95% CI, 0.9–8.5); and >30 years, OR of 5.1 (95% CI, 1.3–19.6), compared with injection drug use of ≤10 years. We examined other variables in the multivariate models for each risk group, including frequency of drug use at 30 days before the interview and the number of times drug paraphernalia were previously used, but their inclusion did not alter the results. Similar but weaker

Table 3. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for human herpesvirus 8 (HHV-8) seroprevalence, by duration of injection drug use and HHV-8 risk group, among 1905 injection drug users in San Francisco.

Years of injection drug use	Women		Heterosexual men		MSM	
	OR (95% CI)[a]	P[b]	OR (95% CI)[c]	P[b]	OR (95% CI)[a]	P[b]
≤10	1.0	.01	1.0	.09	1.0	.08
11–20	2.6 (0.9–7.9)		1.4 (0.6–3.4)		2.5 (1.0–6.3)	
21–30	4.1 (1.3–12.9)		2.0 (0.8–5.1)		2.5 (0.9–7.0)	
31–40	5.8 (1.5–22.7)		2.3 (0.8–6.3)		3.9 (1.1–14.0)	
>40	—		3.0 (0.7–12.0)		—	

NOTE. MSM, men who have sex with men.

[a] Adjusted for age and no. of male sex partners.

[b] P values for trend were calculated using logistic regression analysis.

[c] Adjusted for age and race/ethnicity.

associations were observed after adjustment for age at first use of injection drugs (excluding age from the model). We could not adjust for year of first injection drug use because of the variable's high correlation with duration of injection drug use in each risk group ($r \geq -0.92$).

DISCUSSION

In this study of IDUs from the San Francisco Bay area, HHV-8 seroprevalence was 10% among women, 10% among heterosexual men, and 23% among MSM. These rates are all considerably higher than the HHV-8 seroprevalence of 1%–5% that we and others have observed among US blood donors [16, 22, 23]. We found that HHV-8 seroprevalence increased with the number of years of injection drug use in each of the 3 different groups of IDUs that we defined by sex and sexual orientation (figure 1).

We found no evidence that the association between injection drug use and HHV-8 serostatus resulted from confounding by sexual behavior or other factors. On the contrary, the results for each of the 3 groups became stronger after we controlled for such variables. The relationship was strongest among women, for whom there was a linear association between duration of injection drug use and HHV-8 in both unadjusted and adjusted analyses. For reasons that are unclear, the seroprevalence of HHV-8 among women was inversely related to the number of recent male sex partners. Because it is unlikely that women are protected against HHV-8 infection on that basis, this could be a chance finding. This relationship could be confounded by some other variable, but we found no evidence of such confounding in our multivariate analysis (data not shown).

Because sex between men is a major mode of HHV-8 transmission in the United States [5, 6, 12], it was important to control for that variable in the analysis of data from men. Among heterosexual men (i.e., those who reported a heterosexual orientation and did not report having sex with other men), we conducted a secondary analysis that excluded men who reported receiving cash or drugs in exchange for sex, to eliminate men with unreported homosexual behavior. In this analysis, the trend toward higher HHV-8 seroprevalence with longer IDU duration among heterosexual men increased to the point of statistical significance. Among MSM, adjustment for age and number of recent male sex partners markedly increased the association between HHV-8 seroprevalence and duration of injection drug use.

HHV-8 seroprevalence was more than twice as high among MSM than among women or heterosexual men, which suggests that MSM who use injection drugs risk HHV-8 infection through both sexual and bloodborne transmission. Adjustment for HIV-1 infection status strengthened the association between duration of injection drug use and HHV-8 seropositivity among MSM, but it did not alter the results for women or heterosexual men. Because HIV-1 infection is strongly associated with sexual behavior among MSM [15], HIV-1 serostatus may control confounding by sexual behavior among MSM, but not in the other 2 groups.

HHV-8 has been detected in peripheral blood [24–27], which makes it plausible that bloodborne transmission occurs in injection drug users and transfusion recipients. Transmission to persons with hemophilia through plasma-derived blood products would not be expected, because HHV-8 appears to be primarily cell associated [24, 25]. Studies of recipients of HHV-8–infected blood donations are limited. In the Transfusion Safety Study, 13 recipients of cellular components from HHV-8– (and HIV-1–) seropositive donors were identified, and all remained seronegative for HHV-8 after transfusion [8]. A study in Jamaica followed up 12 recipients of cellular blood products from donors who were seropositive for HHV-8 and found no recipient who was seropositive for HHV-8 [9]. These 2 studies are limited by the small number of subjects enrolled and by the possible poor predictive value of HHV-8 serologic assays in low-prevalence populations, but they suggest that transmis-

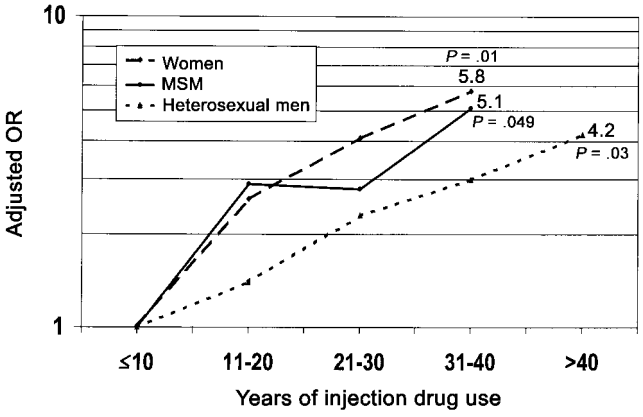

Figure 1. Adjusted odds ratios (ORs) for human herpesvirus 8 (HHV-8) seroprevalence, by duration of injection drug use and HHV-8 risk group, among 1905 injection drug users in San Francisco. ORs for women are adjusted for age and no. of male sex partners. ORs for heterosexual men are adjusted for age and race; men who reported trading sex for money or drugs are excluded from this analysis. ORs for men who have sex with men (MSM) are adjusted for age, no. of male sex partners, and human immunodeficiency virus type 1 infection status. *P* values for trends were calculated using logistic regression.

sion of HHV-8 through blood transfusion, if it occurs at all, is not efficient. Our results are consistent with inefficient bloodborne transmission of HHV-8. For example, female and heterosexual male IDUs in our study had a seroprevalence of only 10% for HHV-8, compared with >90% for HCV. Nevertheless, our study suggests that injection drug use repeated over long periods of time is associated with an increased risk of becoming infected with HHV-8.

The results of previous studies of HHV-8 risk among US IDUs are inconsistent. A study of US women who reported high-risk sexual behavior or drug use found that HHV-8 seropositivity was associated with more frequent recent drug injection [10], but another, similar study did not find a statistically significant association [28]. A study of young MSM from Seattle found that those with a history of injection drug use had a significantly higher seroprevalence of HHV-8 than did those with no history of injection drug use, even after adjustment for sexual behavior and the presence of other sexually transmitted viruses [12]. A study of older MSM from San Francisco, however, reported no significant association after the number of male sex partners was considered [5].

International studies of HHV-8 infection among IDUs are also inconsistent. HHV-8 was more common among IDUs than among blood donors in Spain [29] and in Rome [30], but HHV-8 rates in Sicily were similar among IDUs and in the general population [31]. Investigators from The Netherlands tested specimens collected during 1985–1996 and found that the HHV-8 seroprevalence was 3.4% among men and 1.4% among women, with no evidence of an association with either injection drug use or sharing needles [13]. The difference in the results of these studies could reflect differences in testing algorithms or true geographic/temporal differences in HHV-8 infection prevalences among IDUs.

The chief limitation of the present study is its cross-sectional design. We had retrospective information on duration of injection drug use but only recent information on specific injection practices and sexual behaviors. We were, therefore, unable to fully evaluate the potential confounding effect of long-term sexual behaviors (e.g., lifetime number of sexual partners) that could be associated with an increased risk of HHV-8 infection [7, 12]. These limitations conceivably could have resulted in spurious findings, but, given that our results grew stronger after we controlled for the available data on sexual behavior, it seems more likely that our analyses may have underestimated the association between use of injection drugs and HHV-8 infection. Another limitation is that no reference standard HHV-8 antibody assay exists. We are reassured, however, by the fact that the K8.1 ELISA used in our study has been found to have a relatively high sensitivity and specificity [18, 19] and that the high HHV-8 seroprevalence among MSM in this study is consistent with observations from other studies [5, 16]. Finally, it should be pointed out that, because we recruited active IDUs from 6 selected neighborhoods, the HHV-8 seroprevalence among our subjects is not necessarily representative of that among all IDUs in the San Francisco Bay area.

In conclusion, the number of years of injection drug use was strongly associated with HHV-8 seropositivity in this study. Assuming that longer duration of injection drug use is correlated with exposure to bloodborne agents through the sharing of needles or other injection equipment, these results suggest that HHV-8 is a bloodborne pathogen. Repeated exposure to HHV-8 through injection drug use could increase the prevalence of the virus, and interventions designed to decrease transmission of viruses among IDUs may decrease the spread of HHV-8. Furthermore, if these findings are extrapolated to blood transfusion, our results suggest that acquisition of HHV-8 through transfused blood may be possible. Further research is needed to determine whether that risk truly exists and whether screening donated blood for HHV-8 would be beneficial.

Acknowledgments

We are grateful to Christine Gamache (Viral Epidemiology Section, National Cancer Institute—Frederick, Frederick, MD) and Andrea Stossel (Viral Epidemiology Section, National Cancer Institute—Frederick, and Science Applications International Corporation—Frederick, Frederick), for excellent technical assistance, and Frank Neipel (University of Erlangen, Erlangen, Germany), for providing the K8.1 construct. In addition, we sincerely thank Susan Wilson, Melanie Myers, and Jennifer Mar-

tin (Research Triangle Institute, Washington, DC), for expert technical assistance.

References

1. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science **1994**; 266:1865–9.
2. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma–associated herpesvirus-like DNA sequences in AIDS-related body-cavity–based lymphomas. N Engl J Med **1995**; 332:1186–91.
3. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma–associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood **1995**; 86:1276–80.
4. Carbone A, Gloghini A, Vaccher E, et al. Kaposi's sarcoma–associated herpesvirus DNA sequences in AIDS-related and AIDS-unrelated lymphomatous effusions. Br J Haematol **1996**; 94:533–43.
5. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med **1998**; 338:948–54.
6. Blackbourn DJ, Osmond D, Levy JA, Lennette ET. Increased human herpesvirus 8 seroprevalence in young homosexual men who have multiple sex contacts with different partners. J Infect Dis **1999**; 179:237–9.
7. O'Brien TR, Kedes D, Ganem D, et al. Evidence for concurrent epidemics of human herpesvirus 8 and human immunodeficiency virus type 1 in US homosexual men: rates, risk factors, and relationship to Kaposi's sarcoma. J Infect Dis **1999**; 180:1010–7.
8. Operskalski EA, Busch MP, Mosely JW, Kedes DH. Blood donations and viruses. Lancet **1997**; 349:1327.
9. Engels EA, Eastman H, Ablashi DV, Wilks RJ, Braham J, Manns A. Risk of transfusion-associated transmission of human herpesvirus 8. J Natl Cancer Inst **1999**; 91:1773–5.
10. Cannon MJ, Dollard SC, Smith KD, et al. Blood borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. N Engl J Med **2001**; 344: 637–43.
11. Sosa C, Benetucci J, Hanna C, et al. Human herpesvirus 8 can be transmitted through blood in drug addicts. Medicina **2001**; 61:291–4.
12. Diamond C, Thiede H, Perdue T, MacKellar D, Valleroy LA, Corey L. Seroepidemiology of human herpesvirus 8 among young men who have sex with men. The Seattle Young Men's Survey Team. Sex Transm Dis **2001**; 28:176–83.
13. Renwick N, Dukers NHTM, Weverling GJ, et al. Risk factors for human herpesvirus 8 infection in a cohort of drug users in The Netherlands, 1985–1996. J Infect Dis **2002**; 185:1808–12.
14. Watters JK, Estilo MJ, Clark GL, Lorvick J. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. JAMA **1994**; 271: 115–20.
15. Kral AH, Bluthenthal RN, Lorvick J, Gee L, Bacchetti P, Edlin BR. Sexual transmission of HIV-1 among injection drug users in San Francisco, USA: risk-factor analysis. Lancet **2001**; 357:1397–401.
16. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma–associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med **1996**; 2:918–24.
17. Smith NA, Sabin CA, Gopal R, et al. Serologic evidence of human herpesvirus 8 transmission by homosexual but not heterosexual sex. J Infect Dis **1999**; 180:600–6.
18. Engels EA, Whitby D, Goebel PB, et al. Identifying human herpesvirus 8 infection: performance characteristics of serological assays. J Acquir Immune Defic Syndr **2000**; 23:346–54.
19. Engels EA, Sinclair MD, Biggar RJ, et al. Latent class analysis of human herpesvirus 8 assay performance and infection prevalence in sub-Saharan Africa and Malta. Int J Cancer **2000**; 88:1003–8.
20. Greenland S, Rothman JK. Introduction to stratified analysis. In: Rothman JK, Greenland S, eds. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, **1998**:256–9.
21. Fisher LD, Van Belle G. Discrimination and classification. In: Fisher LD, Van Belle G, eds. Biostatistics: a methodology for the health sciences. New York: John Wiley & Sons, **1993**:634–41.
22. Simpson GR, Schulz TF, Whitby D, et al. Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet **1996**; 348: 1133–8.
23. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med **1996**; 2:925–8.
24. Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet **1995**; 346:799–802.
25. Decker LL, Shankar P, Khan G, et al. The Kaposi sarcoma–associated herpesvirus (KSHV) is present as an intact latent genome in KS tissue but replicates in peripheral blood mononuclear cells of KS patients. J Exp Med **1996**; 184:283–8.
26. Blackbourn DJ, Ambroziak J, Lennette E, Adams M, Ramachandran B, Levy JA. Infectious human herpesvirus 8 in a healthy North American blood donor. Lancet **1997**; 349:609–11.
27. Wit FW, Sol CJ, Renwick N, et al. Regression of AIDS-related Kaposi's sarcoma associated with clearance of human herpesvirus-8 from peripheral blood mononuclear cells following initiation of antiretroviral therapy. AIDS **1998**; 12:218–9.
28. Greenblatt RM, Jacobson LP, Levine AM, et al. Human herpesvirus 8 infection and Kaposi's sarcoma among human immunodeficiency virus–infected and –uninfected women. J Infect Dis **2001**; 183:1130–4.
29. Gambus G, Bourboulia D, Esteve A, et al. Prevalence and distribution of HHV-8 in different subpopulations, with and without HIV infection, in Spain. AIDS **2001**; 15:1167–74.
30. Rezza G, Lennette ET, Giuliani M, et al. Prevalence and determinants of anti-lytic and anti-latent antibodies to human herpesvirus–8 among Italian individuals at risk of sexually and parenterally transmitted infections. Int J Cancer **1998**; 77:361–5.
31. Perna AM, Bonura F, Vitale F, et al. Antibodies to human herpesvirus type 8 (HHV 8) in general population and in individuals at risk for sexually transmitted diseases in Western Sicily. Int J Epidemiol **2000**; 29:175–9.